

In response to the Examiner's comments regarding the possible duplication between claim 1 and claims 2 and 5, please note that claims 1, 2 and 5 have been cancelled pursuant to the above.

The applicants respectfully traverse the rejection of claims 1-3 and 5 under 35 USC 102(b) in view of Asami et al. This reference does not anticipate the presently claimed invention.

However, please note that claims 1-3 and 5 have been cancelled thus rendering this rejection to be moot. Withdrawal of the rejection is according requested.

The applicants respectfully traverse the rejection of claim 4 under 35 USC 103(a) in view of Asami et al. in view of Pierpaoli et al. The cited references do not make the presently claimed invention to be obvious.

The applicants assert that the use of astaxanthin and/or its ester or of a composition of astaxanthin and/or its ester and melatonin for normalizing circadian rhythm is not disclosed or suggested by the teachings of Asami et al., with or without the teachings of Pierpaoli.

New claims 6-10 recite a second-indication of astaxanthin and/or an ester thereof which are not suggested or made obvious by Asami and/or Pierpaoli.

Asami discloses that astaxanthin and/or its ester is an effective ingredient for an anti-stress composition, and that stress disorders and other related disorders are believed to result in an inability of the body to maintain homeostasis.

The teachings of Pierpaoli do not remedy the deficiencies of Asami.

The Office Action suggests that only a single cause exists for the disturbance of circadian rhythm, namely, stress. However, the applicants submit that stress is not the sole cause of such disturbance.

For the presently claimed invention, the circadian rhythm normalizing activity of astaxanthin or astaxanthin plus melatonin was determined and confirmed by experimentation with rats that were kept under stress-free conditions (as described in the present specification). Specifically, the daily movements of rats that were fed under normal conditions and kept free from stress, were measured (see Examples in present specification). Tests were conducted to determine improvements in or normalizing of circadian rhythm with test animals fed under stress-free conditions. However, the experiments were not conducted to determine normalization of disturbance of circadian rhythm caused by stress.

In referring the description of Examples in the specification, please note the following:

(1) As explained in Example 1, the influence of astaxanthin on daily movements was investigated in rats. The investigation provided the following results.

(a) Astaxanthin did not affect the total amount of movement in comparison with the control (no astaxanthin is ingested) (Fig. 1).

(b) The ratio (%) of movement in the light period decreased in astaxanthin ingested rats as compared to the control group. That is, the ingestion of astaxanthin caused a decrease in the activity of rats in the light period, and an increase in the activity of rats in the dark period.

From the results (a) and (b), it is considered that the ingestion of astaxanthin can normalize or improve the circadian rhythm of rats kept under normal (stress-free) conditions. This activity of astaxanthin is suggested by the prior art references, and the applicants submit that this type of activity is not the same as that of Asami.

(2) As explained in Example 2, the synergistic effects of astaxanthin and melatonin were investigated and the following results obtained.

(a) No significant differences were noted among the averages of the total amount of movement in the four groups shown in Figure 4. These four groups are an astaxanthin and melatonin group, an astaxanthin alone group, a melatonin alone group, and the control group.

(b) The ratio (%) of movement in the light period decreased in each of the astaxanthin alone ingested group and the melatonin alone ingested group as compared to the control group. In the astaxanthin and melatonin ingested group a ratio of movement in the light period significantly decreased (Figure 5 and Figure 8).

From the results (a) and (b) above, one may deduce that the simultaneous ingestion of astaxanthin and metatonin acts synergistically to normalize or improve circadian rhythm of rats which are kept under normal (stress-free) conditions. This synergistic activity of astaxanthin and melatonin is no where disclosed or suggested by the prior art references.

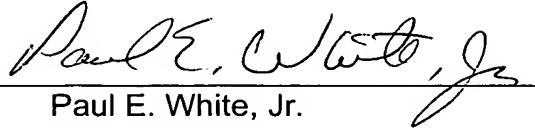
(3) As described in Example 3, when melatonin and  $\alpha$ -tocopherol are simultaneously ingested, no significant effect of enhancement of the circadian rhythm normalizing action caused by melatonin was observed, when compared to ingestion of a combination of melatonin and astaxanthin. This occurred despite the fact that both  $\alpha$ -tocopherol and astaxanthin exhibit anti-oxidant activity.

Accordingly, the applicants submit that the presently claimed invention is fully allowable under Section 10-3(a) in view of the prior art.

In view of the above, it is believed that this application is in condition for allowance and a Notice to that effect is respectfully requested.

Respectfully submitted,

Manelli Denison & Selter, PLLC

By 

Paul E. White, Jr.

Reg. No. 32,011

Tel. No.: (202) 261-1050

Fax No.: (202) 887-0336

2000 M Street, N.W.  
Seventh Floor  
Washington, D.C. 20036  
(202) 261-1000

**APPENDIX**

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Proposed Amendments To Claim 4 Showing Deletions And Insertions.

Claim 4. (Amended) A composition [comprising astaxanthin and/or an ester thereof and melatonin, adapted to enhance a hyponotic action and/or a] for normalizing circadian rhythm [normalizing action of melatonin as a result of ingestion of the] which comprises astaxanthin and/or ester thereof and melatonin [in combination, and aimed at preventing and alleviating sleep disorder and various diseases due to disturbance of a circadian rhythm].